Modeling to Incorporate Defense Mechanisms into the Estimation of Dose Responses

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Several adverse health effects (including cancer and noncancer effects) may be the result of an imbalance between exogenous and endogenous invading substances and defense mechanisms. In these cases the probability of an adverse effect depends on how much the exposure to a substance increases or decreases the number of defenders or their efficiency as well as increasing or decreasing the number of invaders. Rather than using a dose scale such as parts per million or milligram/kilogram/day in these cases, dose–response models can directly incorporate the impact of defense mechanisms by using a dose scale that corresponds to the number of invaders that break through the defenders and become free to do their damage. The number of breakthroughs at a specific age, the cumulative number of breakthroughs by a specific age, or the cumulative number of breakthroughs in a window of time would usually be the appropriate age-dependent dose. Although a lifetime average daily dose level can be used as a surrogate for an age-dependent dose in simplistic dose–response models, the age-dependent dose itself can be used in more biologically based models that include time, reflect the key role of feedback mechanisms, and treat the human body as an age-dependent dynamic system responding to internal and external stimuli and not as a system at equilibrium. Some illustrative biologic examples of defense mechanisms and invader–defender interactions are presented. Several numerical examples are given in which the dose incorporates the age-dependent effects of a substance on the number of invaders, the number of defenders, and/or the defenders' efficiencies. — *Environ Health Perspect* 106(Suppl 1):341–348 (1998). *http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-1/341-348sielken/abstract.html*

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Introduction

Health is a balance between harmful and helpful forces. This balance can be modeled by considering the relative proportions of invaders and defenders and an individual defender's efficiency in defeating a single invader.

Several adverse health effects (including both cancer and noncancer effects) may be the result of an imbalance between exogenous and endogenous invading substances and defense mechanisms. Opposing forces are involved in most normal physiologic processes as well as in abnormal processes such as cancer, infectious diseases, immune system disorders, neurotoxicity, organ toxicity, adverse reproductive effects, teratogenesis, and developmental problems.

Most chemicals are considered to be invaders although their metabolism by defense enzyme systems is usually to less toxic metabolites. The cytochrome P450 system is one such system that is induced at low-level exposures—in some cases this is the earliest measure of exposure. This induction is also related to the increased synthesis of ascorbic and glucaric acids in the liver, and both of these acids can inhibit certain steps of the carcinogenic process. Another important defense mechanism in this process is cell-cycle arrest or apoptosis depending on the degree of activation of the *p53* gene. There are many examples of enhanced defenses relating to the immune system. The responses of the whole organism can be modified by lifestyle changes, regular aerobic exercise, diet content, caloric restriction, supplementation with antioxidants (including green tea and other plant sources of flavonoids), degree of stress, etc.

Some of these effects are almost qualitative; e.g., inhibition of the carcinogenic response by caloric restriction. There also are some examples in which exposure to a chemical leads to an adverse health effect, but if that exposure is preceded by exposure to some other specific chemical, there is no adverse health effect. In such cases the other specific chemical is enhancing some defense mechanisms. It long has been known that many defense mechanisms tend to become less effective with age and that when enhanced they may increase average life span but not necessarily maximum life span.

Defense mechanisms should be an important component of risk assessment and dose–response modeling. Inclusion of defense mechanisms and the whole invaders/defenders concept provides an opportunity to make dose–response models more biologically based and to incorporate more of the available scientific data. Furthermore, their inclusion can have a significant impact on the shape of dose-response relationships. When defense mechanisms are stimulated at low exposure levels, protective or hormetic responses are possible. Historically, the saturation of enzyme systems has been considered the major source of potential nonlinearity and the role of key defense mechanisms induced by low levels of exposure has been ignored.

This paper reviews the invaders/defenders concept developed in earlier papers (*1–4*), illustrates how the concept can be incorporated into dose–response modeling, provides numeric examples, and indicates potential generalizations and avenues of further research. The intent of this paper is to make the invaders/defenders concept a practical tool for more biologically based dose–response modeling and for generating research strategies.

Specific Biologic Examples

In risk assessment some inherent mathematical assumptions have had a major influence on the models used. For instance, a body is considered to continue in its current state of rest or uniform motion unless it is compelled to change that state by forces impressed on it. Thus, it is assumed that all bodies or animals in a model are in a state of equilibrium and there is only one force (i.e., carcinogen exposure) acting on them. This is not biologic reality. Several factors (including exposure and defense mechanisms) may change the characteristics of the biologic system. These multiple

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changes occur in many ways, and what is observed is only the net result of complex interactions that change over time. It may only be possible to model such complex processes approximately, but at least the additional factors known to exist should be considered. It must also be acknowledged that all bodies are not equal, for in biology major species and strain differences in response may reflect major differences in defense mechanisms.

Two different specific biologic examples are given to demonstrate how the characteristics of biologic systems may change.

Example 1

In initiation–promotion protocols for the production of tumors (particularly skin and liver), an initiating dose of a compound such as diethylnitrosamine is given, followed several days later by the longer-term administration of a promoter. This protocol gives a tumor yield when administration of either the initiator or promoter separately would not. Phenobarbital is a drug used in many such initiation–promotion protocols.

When phenobarbital alone is administered to rats, there is an initial burst of DNA synthesis of a few days, but within 1 week the animals become refractory to the toxicant with respect to DNA synthesis. If an initiator is administered after phenobarbital (or promoter), the rats are also refractory to the initiator, which implies that there has been an increase in defenses. There is a time sequence to this because when the initiator is given before phenobarbital and phenobarbital is given either continuously or only intermittently, the latter sequence is more effective in inducing DNA synthesis. This suggests that the refractory state is readily reversible (*5*). Among the biochemical events that occur with phenobarbital exposure are induction of the cytochrome P450 enzymes, a reduction in liver vitamin E concentration, and an increased synthesis of ascorbic and glucaric acids. All these compounds are antioxidants and can inhibit chemically induced DNA synthesis. Of course, enzyme induction is also a form of self-induced defense. Thus, exposure has changed the nature of the defenses.

Example 2

The carcinogenic response may be profoundly altered by the quantity and composition of diet. U.S. National Toxicology Program researchers have been concerned about the increasing incidence of liver tumors in their rodent bioassays and have considered increasing the amount of vitamin E in the diets used. In essence this would modulate a carcinogenic response by increasing the defense mechanisms. However, it may not be as effective as other interventions. In a recent study (J Klaunig, unpublished data) that examined the relationship between dieldrin-induced mouse liver tumors in the presence or absence of vitamin E supplementation, it was found that although at 10 months vitamin E appeared to be have reduced the tumor incidence in both control and dieldrin-treated animals, by 18 months it had actually increased the proportion of control animals with liver tumors and had not protected the dieldrin-exposed animals. Vitamin E decreased the incidence of apoptotic nuclei by about 75% in hepatic adenomas, suggesting that an apparent defense mechanism may have paradoxic effects in tumor tissue. Furthermore, the liver glutathione concentration, which falls by a factor of 4 or 5 in older animals, was high in dieldrin-induced liver tumors. Thus, the ability of animals to utilize their defense mechanisms appears to be age dependent and tumors may acquire more efficient defenses than their hosts.

Examples such as these show that the carcinogenic process is subject to substantial forces in both directions and also that the impact of these forces may be time dependent.

Invaders and Defenders

The invaders/defenders concept is quite intuitive. Invaders (e.g., molecules of a toxic chemical) enter the body or a specific tissue or cell and try to attack a system, a tissue, or a cell component. Each defender (e.g., an individual molecule or larger component of the defense mechanisms of the cell, tissue, or body) has a probability of preventing an individual invader from successfully attacking its target. The defeat of an invader is a broad idea encompassing the interaction of molecules, cells like phagocytes, the storing of damage in a harmless form such as in the case of cell-cycle arrest, or the elimination of damage (e.g., apoptosis).

For the numerical examples in this paper, the rules of combat between invader and defender are as follows; however, these rules could be modified if appropriate. An invader must successfully escape defeat at the hands of each available defender. When an invader confronts a defender, the defender has a specified probability of defeating (neutralizing or destroying) the invader—for simplicity this probability is called the defender's efficiency and is denoted mathematically as *DE*. Thus, if the initial number of defenders is *ND*, the probability that the first invader is not defeated by any of the initial *ND* is $(1-DE)^{ND}$. If the invader is not defeated by any available defender, the invader is said to have broken through the defense system and is free to damage its target. If an invader is defeated by a defender, that defender is used up and is not available to confront the next invader. Thus, if the number of invaders, *NI*, is large and several of the early invaders are defeated, later invaders face fewer defenders and have a greater probability of breakthroughs. The total number of breakthroughs, *NB*, is a random variable that depends on the *NI*, the *ND*, and the *DE*.

Therefore, for a given number of invaders the number of breakthroughs increases as the number of defenders decreases and vice versa (Figure 1). Similarly, the number of breakthroughs increases as the individual defender's efficiency decreases and vice versa (Figure 2).

Monte Carlo simulation routines can be used to determine large numbers of random realizations of the age-dependent number of breakthroughs as well as to estimate the age-dependent expected number of breakthroughs (i.e., the mean number of breakthroughs at a particular age). The age-dependent expected number of breakthroughs is an age-dependent single number summarization of the stochastic interaction between invaders and defenders and the resultant random number of breakthroughs. In the discussions that follow, the term number of breakthroughs is interpreted as either a large number of random realizations of the age-dependent series of numbers of breakthroughs or the age-dependent expected number of breakthroughs. In the numerical examples the number of breakthroughs is the age-dependent expected number of breakthroughs.

Incorporating the Concept of Invaders and Defenders into Dose–Response Models

A More Biologically Relevant Dose Scale

Most dose–response models for adverse health effects are either strictly curve-fitting models or rough mathematical representations of a general mechanistic hypothesis (e.g., a multistage model for carcinogenesis). In either case, the dose in these models can

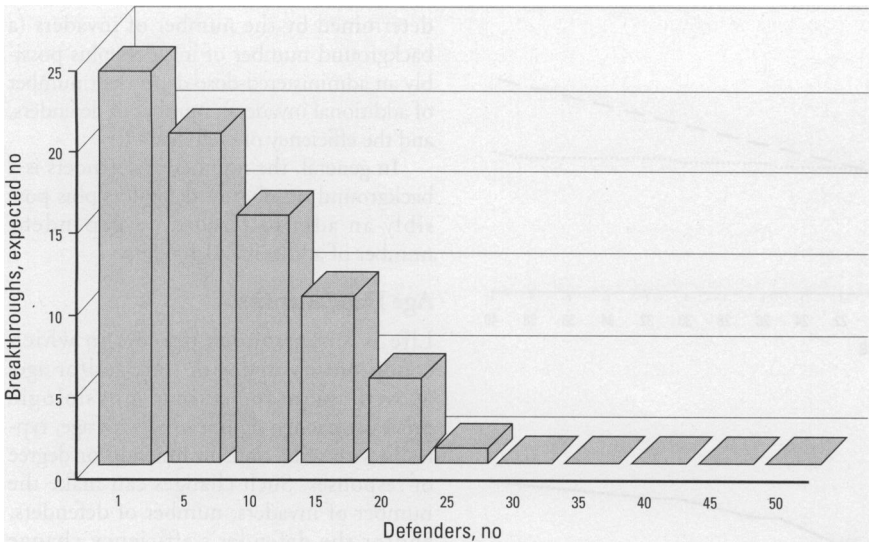

Figure 1. An example of the impact of the number of defenders on the expected number of breakthroughs. Each defender has a 50% chance of defeating an invader (number of invaders = 25).

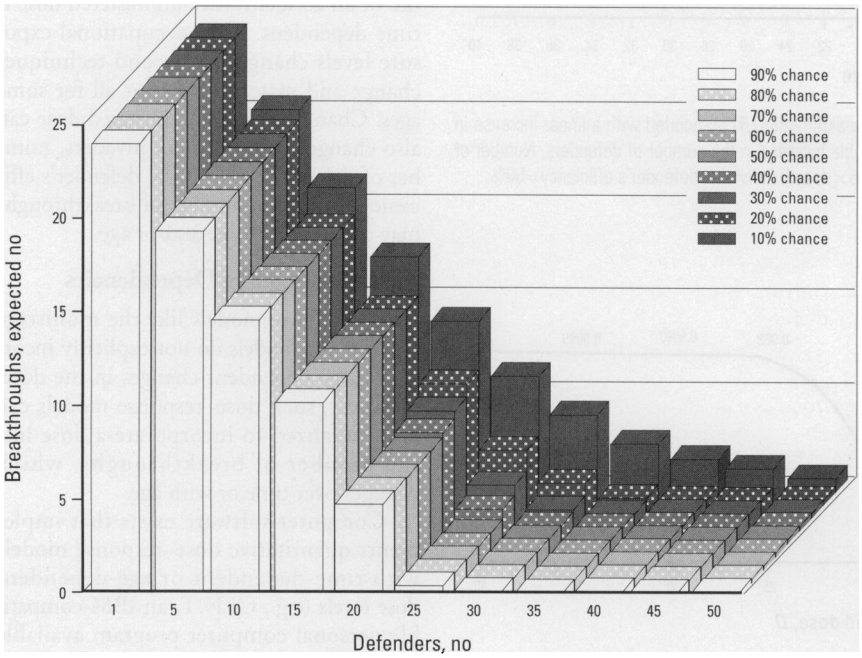

Figure 2. An example of the impact of an individual defender's efficiency (chance) on the expected number of breakthroughs. Each defender has a chance of defeating an invader (number of invaders = 25).

be any biologically relevant characteristic of an exposure. The most common and most simple dose scale is the administered or applied dose (e.g., milligram/kilogram/day or parts per million). However, this dose scale reflects the least amount of information about the exposure. Alternative dose scales offer an important opportunity to incorporate more biologic information into dose–response modeling and result in a more biologically based dose–response model. A better alternative dose scale than the administered dose often is the delivered dose, which corresponds to the amount of the chemical or its metabolite that actually reaches the target tissue. The objective of physiologically based pharmacokinetic models is to determine the delivered dose. However, an even better alternative dose scale is the biologically effective dose, which reflects not only the amount delivered to the target tissue but also the net amount of some relevant activity related to the health effect that occurs after delivery. When invaders and defenders are involved, a relevant biologically effective dose is the expected number of breakthroughs corresponding to the exposure.

A practical means of incorporating the role of invaders and defenders into the dose–response modeling for an adverse health effect is by defining the dose in the dose–response model to be the expected number of breakthroughs corresponding to the exposure. This dose scale reflects the exposure's impact on the number of invaders, the number of defenders, and the individual defender's efficiency.

Dose Equal to the Number of Breakthroughs

Even the simplest dose–response models like the linear multistage model and the one-hit model for cancer can be made to at least modestly reflect the role of invaders and defenders if the dose in these models is defined to be the number of breakthroughs. Specifically, these two dose–response models would become

Probability of adverse health effect (P) at administered dose D =

$$1 - \exp\{-[\alpha_0 + \alpha_1 \times (NB \text{ at } D)]\}$$

or, equivalently,

$$P(D) = 1 - \exp\{-[\alpha_0 + \alpha_1 \times NB(D)]\}.$$

Figures 3 and 4 give a simple illustration of this type of dose relationship; i.e., how the probability $P(D)$ of an adverse health effect would change as the administered dose D changes. In Figure 3A the number of invaders increases linearly with D, whereas there is a saturable increase in the number of defenders with D. Figure 3B shows how the resulting number of breakthroughs changes as D changes. Figure 4 shows a plot of the resulting dose–response model (with $\alpha_0 = 0$ and $\alpha_1 = 1$)

$$P(D) = 1 - \exp\{-NB(D)\}.$$

The shape of this linear multistage or one-hit model is linear in the dose $NB(D)$. However, the shape of the model versus the administered dose D clearly is nonlinear and hormetic because of the decreasing probability of an adverse health effect for D between $D = 0$ and $D = 10$.

The shape and low-dose behavior of a dose–response relationship with the dose defined as the number of breakthroughs is

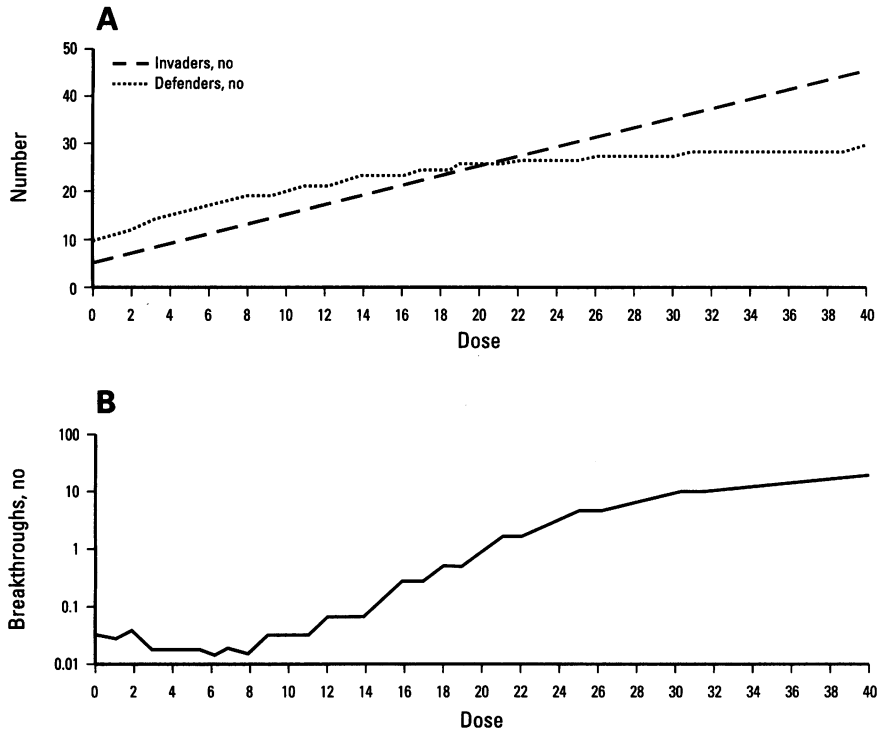

Figure 3. An example of a hormetic effect on the number of breakthroughs (*B*) associated with a linear increase in the number of invaders with dose (*A*) accompanied by a saturable increase in the number of defenders. Number of invaders = 5 + dose; Number of defenders = 10 + 20[1 − exp(−0.75 × dose)]; individual defender's efficiency = 50%.

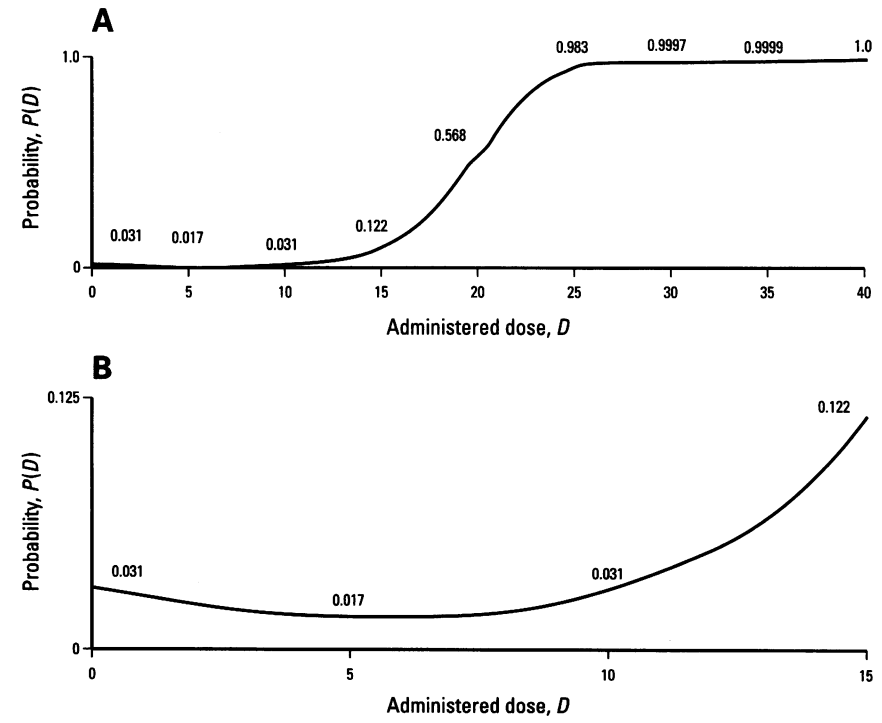

Figure 4. An example of a dose–response model where the impact of the administered dose is on the number of invaders, defenders, and breakthroughs as shown in Figure 3. (*B* is an enlargement of the lower dose portion of *A*.)

determined by the number of invaders (a background number of invaders plus possibly an administered-dose-dependent number of additional invaders), number of defenders, and the efficiency of each defender.

In general, the number of defenders is a background number of defenders plus possibly an administered-dose-dependent number of additional defenders.

Age Dependencies

Life is a continuous process in which conditions change with time and/or age. Most human and animal physiologic processes change significantly with age, typically with reductions in function or degree of responses. Such changes can make the number of invaders, number of defenders, and/or the defender's efficiency change with age. Exposure levels and the administered dose can change over time. If exposures levels relate to a specific event like a fire or an accident, the administered dose is time dependent. Also, occupational exposure levels change as jobs and techniques change and may not occur at all for some ages. Changes in the administered dose can also change the number of invaders, number of defenders, and/or the defender's efficiency. Thus, the number of breakthroughs may change with time and/or age.

Incorporating Age Dependencies

Dose–response models like the multistage and one-hit models do not explicitly incorporate age-dependent changes in the dose. However, such dose–response models can be generalized to incorporate a dose like the number of breakthroughs, which changes over time or with age.

Computer software exists that implements quantitative dose–response models with time-dependent or age-dependent dose levels (e.g., GEN.T, an IBM-compatible personal computer program available from Sielken, Inc., Bryan, TX). Software is available from the authors into which the components necessary to derive an age-dependent number of breakthroughs can be explicitly entered and the age-dependent number of breakthroughs determined. Currently these age-dependent components are the background number of invaders, background number of defenders, defender efficiency, and administered dose, as well as the functional relationship between an administered dose level and the additional numbers of invaders and defenders.

The dose–response models incorporating the invaders/defenders concept can be used for hypothesis generation and exploratory

evaluation of hypothetical scenarios. In addition, software is available from the authors that can link dose–response models with maximum likelihood estimation techniques to fit observed data to dose–response models incorporating invaders and defenders and their time and/or age dependencies.

Sample Dose–Response Models

The invaders/defenders concept can be used with any existing dose–response model. This is done by defining the dose in the models to be the number of breakthroughs. Obviously models will be more biologically realistic if the dose–response model allows an age-dependent dose scale in which the full age-dependent nature of the number of breakthroughs can be incorporated rather than a single-number summary of the number of breakthroughs.

Two additional examples of general dose–response models including the invaders/defenders concept and an age-dependent number of breakthroughs are described in this section.

As is frequently done in human epidemiologic modeling, the age-dependent probability of an adverse health effect can be modeled as a proportional hazards model in which the age-dependent multiplier of the age-dependent background hazard rate is a function of the age-specific dose—here the age-specific dose would be the age-specific number of breakthroughs. In such dose-response models, the probability ($P[T; D(t), t = 0,..., T]$, which for simplicity is denoted by $P[T; D(t)]$), of a specified adverse health effect by age T when the age-dependent administered dose is $D(t)$ at age t is

$$P[T; D(t)] = 1 - \exp\{-\int_0^T \lambda_0(t) \times PHM[t; D(t)]\,dt\}$$

where the proportional hazards multiplier (PHM) is

$$PHM[t; D(t)] = \exp\{\alpha_0 + \alpha_1 \times [NB(t)] + \alpha_2 \times [NB(t)]^2 + ...\}$$

in which the age-dependent and administered-dose-dependent number of breakthroughs at age t, say $NB[t; D(t)]$, has been denoted by $NB(t)$.

$NB(t)$, the number of breakthroughs at age t, is a function of the history of the number of invaders, number of defenders, and individual defender's efficiency up to age t. NI and ND at age t could be the sum of a background number (NI_0 and ND_0, respectively) and an additional administered-dose-dependent number (ANI and AND, respectively); for example,

$$NI[t; D(t)] = NI_0(t) + ANI[D(t)]$$

$$ND[t; D(t)] = ND_0(t) + AND[D(t)].$$

Alternatively, the age-dependent probability of an adverse health effect can be modeled with the hazard rate for the adverse health effect being the sum of an age-dependent background hazard rate and an administered-dose-dependent hazard rate. The administered-dose-dependent hazard rate would depend on the administered dose through the impact of the administered dose on the number of breakthroughs. In such dose–response models, the probability ($P[T; D(t)]$) of a specified adverse health effect by age T when the age-dependent administered dose is $D(t)$ at age t is

$$P[T; D(t)] = 1 - \exp\{-\int_0^T \lambda_0(t) + \lambda_{Add}[t; D(t)]\,dt\}$$

where the administered-dose-dependent hazard rate is

$$\lambda_{Add}[t; D(t)] = \alpha_0 + \alpha_1 \times [NB(t)] + \alpha_2 \times [NB(t)]^2 + ...$$

Model Components and Their Combination

The output of the dose–response model is the probability of a specified adverse health effect for a specified administered dose. This output will usually be expressed as an added risk, namely,

$$\text{added risk at age } T = P[T; D(T)] - P[T; 0],$$

which is the increase in the probability of a specified adverse health effect for an administered dose history of $D(T)$ compared to the same probability for dose zero.

The ultimate input to the dose–response model is the number of breakthroughs. The model components and their combination to determine the added risk of a specified adverse health effect are illustrated in Figure 5. The inputs determining the number of breakthroughs are the age-dependent background number of invaders, age-dependent background number of defenders, age-dependent individual defender's efficiency, age-dependent relationship between the administered dose and additional number of invaders, age-dependent relationship between administered dose and additional number of defenders, and age-dependent administered dose.

The impact of the age-dependent administered dose is to determine the age-dependent additional number of invaders and defenders.

The age-dependent additional number of invaders and defenders combine with their respective background numbers to determine the age-dependent total number of invaders and the age-dependent total number of defenders.

The age-dependent total number of invaders and defenders and the age-dependent individual defender's efficiency combine to determine the age-dependent number of breakthroughs.

Finally, the age-dependent number of breakthroughs determines the age-dependent added risk of a specified adverse health effect.

Numerical Examples

For the invaders/defenders concept to become a practical tool for dose–response estimation and generation of research strategies, tools must exist that allow a risk assessor or researcher to determine the quantitative values of the numbers of breakthroughs and added risks associated with different specific numerical values for the components of the invaders/defenders paradigm. Figures 6 through 11 are specific numerical examples of applying the general methodology illustrated in Figure 5 for specifying the components of the invaders/defenders paradigm and combining them to determine the added risk of a specified adverse health effect.

Although the primary importance of Figures 6 through 11 is to prove that the invaders/defenders concept is a practical, implemented, and available approach to dose–response estimation and generation of research strategies, the examples in the figures are themselves somewhat interesting. They illustrate what happens in several situations. For example,

- when the number of defenders decreases with age (Figure 6);
- when the number of defenders is affected by feedback (Figure 7);
- when the administered dose has different age dependencies (Figure 8);
- when the individual defender's efficiency decreases with age (Figure 9);
- when the administered dose impacts the numbers of both the invaders and

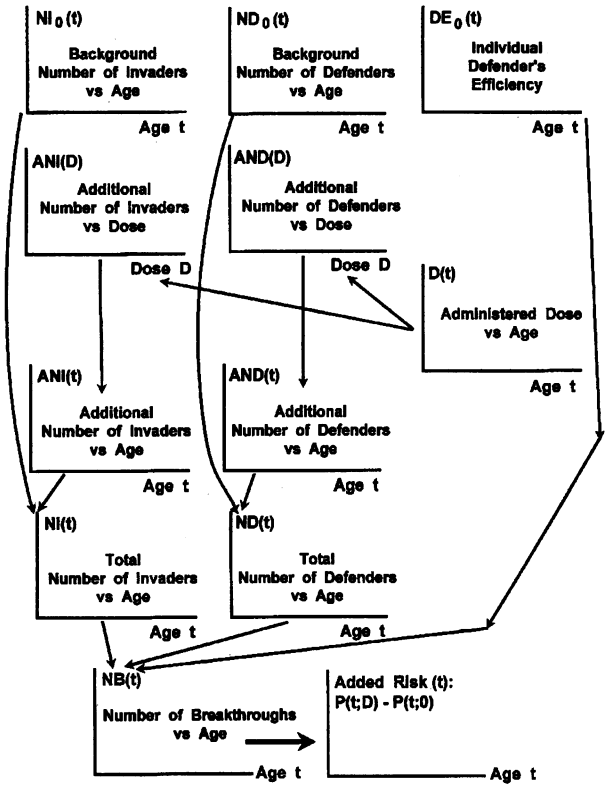

Figure 5. Invader/defender components and their combination into a dose–response model-based prediction of the added risk of a specified adverse health effect.

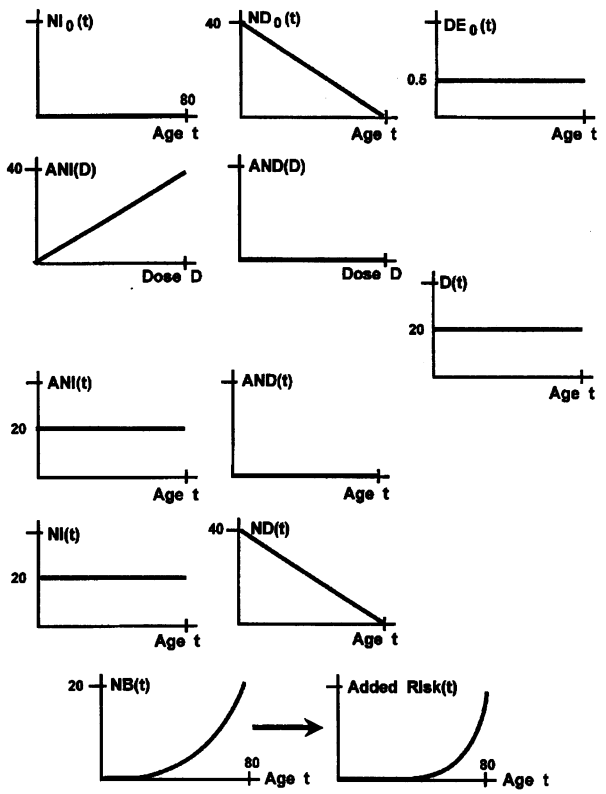

Figure 6. Example 1: number of defenders decreasing with age.

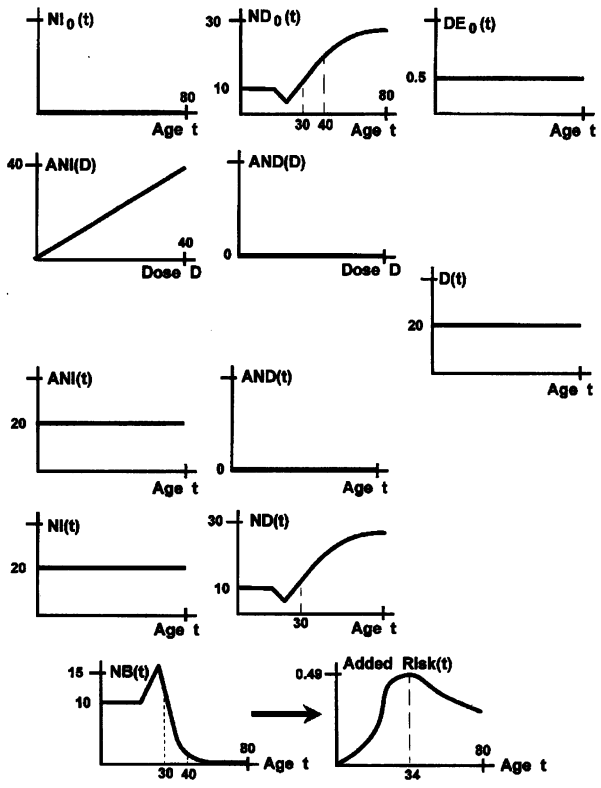

Figure 7. Example 1 (modified): number of defenders affected by feedback.

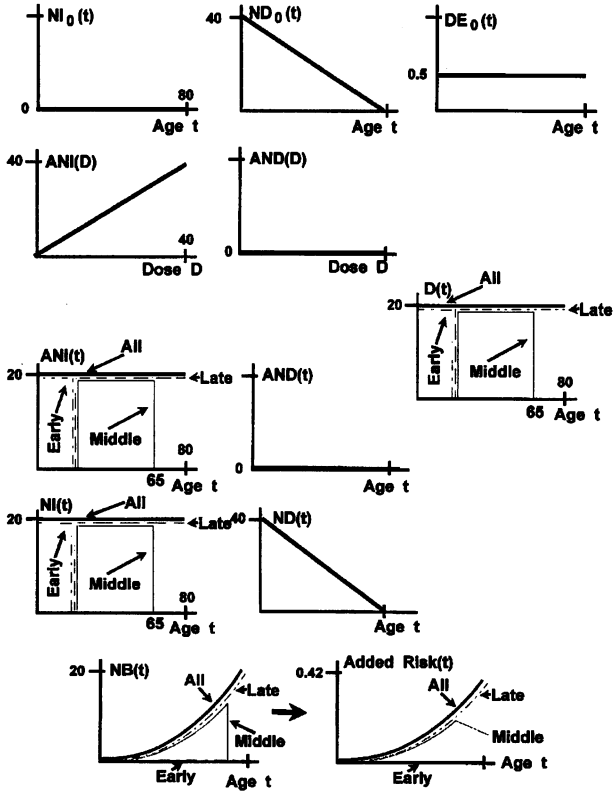

Figure 8. Example 1 (continued): impact of age-dependent administered dose.

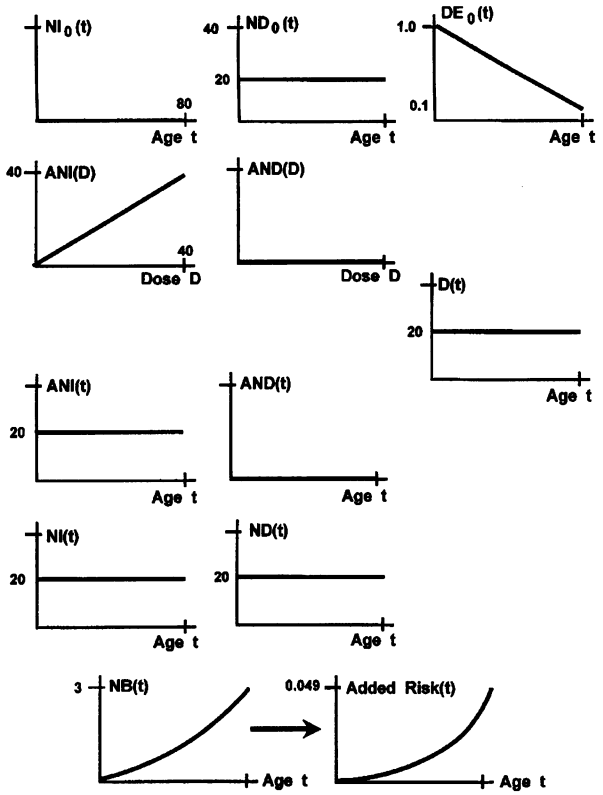

Figure 9. Example 2: individual defender's efficiency decreasing with age.

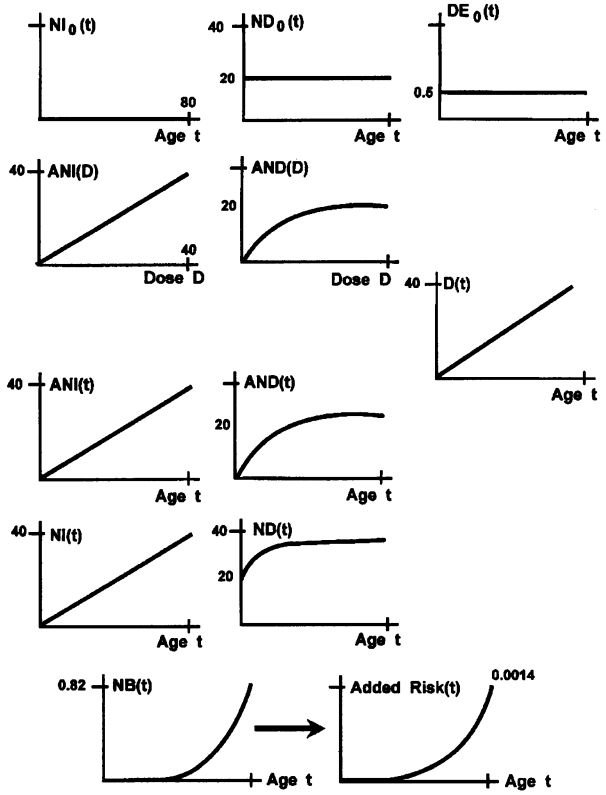

Figure 10. Example 3: an age-dependent administered dose affecting the number of invaders and defenders.

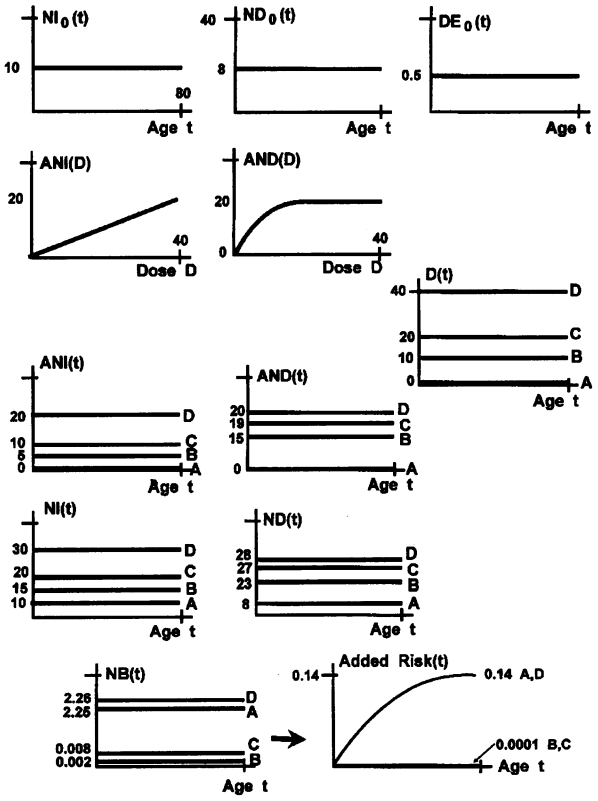

Figure 11. Example 4: impact of magnitude of administered dose.

defenders and the administered dose is age dependent (Figure 10); and
- when the administered dose affects the numbers of both the invaders and defenders and the magnitude of an age-independent administered dose changes (Figure 11).

Generalizations

There are several generalizations of the implementation of the invaders/defenders concept described above. One generalization would be for $D(t)$ in the dose–response models incorporating invaders and defenders and their age dependencies to be expanded to include any one of the following alternatives: $D(t)$, administered dose at age t; $D(t)$, cumulative administered dose by age t; $D(t)$, cumulative administered dose in a window of ages (e.g., from t–20 to t); etc.

A second generalization would be for $NB(t)$ in the dose–response models incorporating invaders and defenders and their age dependencies to be expanded to include any one of the following alternatives: $NB(t)$, number of breakthroughs at age t; $NB(t)$, cumulative number of breakthroughs by age t; $NB(t)$, cumulative number of breakthroughs in a window of ages (e.g., from t–20 to t); etc.

A third possible generalization would be for the individual defender's efficiency to be administered-dose dependent if the administered dose facilitates or hinders some ancillary attribute relevant to the defender's successful defeat of an invader. For example, the defender might work in conjunction with an enzyme and the administered dose might affect the level of that enzyme.

Discussion

Incorporation of defense mechanisms and the invaders/defenders concept is an important new approach to developing more biologically based dose–response models. The invaders/defenders concept provides an opportunity to incorporate time and age dependencies, the body as a dynamic system, and feedback mechanisms into the model.

Like the innovative Moolgavkar–Venzon–Knudsen models reflecting cell proliferation in cancer dose–response modeling, the incorporation of the invaders/defenders concept allows the body to be more realistically treated as an age-dependent dynamic system responding to external and internal stimuli rather than a system at equilibrium.

Although feedback mechanisms were not specifically introduced into the above examples, the invaders/defenders concept can easily incorporate feedback mechanisms. For example, the number of defenders, $ND(T)$, at age T could be treated as dependent on the history (between $t = 0$ and $t = T$) of the number of invaders and the history of the number of defenders. For instance, $ND(T)$ could be proportional to the cumulative number of breakthroughs

$$\int_0^T NB(t)\, dt$$

or the largest number of breakthroughs in the past

$$\max_{0 \le t \le T} [NB(t)].$$

Conclusions

Species and strain differences in the frequencies of adverse health effects could be explained by species and strain differences in the number of invaders, the number of defenders, the individual defender's efficiency, their age dependencies, and their administered-dose dependencies.

The concept of invaders and defenders is presented to stimulate interest in the multifactorial nature of the dose and dose-response modeling of adverse health effects and to highlight the fact that defense mechanisms can play a major role in determination of the frequency of adverse health effects. It can be predicted, for instance, that an increase in tumor incidence may occur without additional exposures to carcinogens if an organism's defenses are depleted. This side of the balance is not normally considered in the modeling of the carcinogenic process. We were surprised by the number of factors that may produce hormetic effects in simulations. This suggests that hormesis may be more widespread than generally recognized but that it may be confined to a range of doses that perhaps fall below those commonly employed in chronic bioassays, particularly if only the maximum tolerated dose and half this dose are used.

In the past it has been assumed (with less than critical reasoning) that for some adverse health effects like cancer, low-dose linearity would be a general phenomenon. The invaders/defenders model indicates that even if the formation of DNA adducts is linear, there are many other factors that may lead to low-dose nonlinearity or even hormetic responses.

The concept of invaders and defenders has a high degree of practical importance for the evolution of attitudes toward the reduction of the incidence of adverse health effects. It demonstrates that attention to factors that increase defenses may be as important as the search for environmental toxic chemicals. Specifically, defense mechanisms are especially important because they may modify the effects of multiple toxic chemicals. More attention to the defense systems that affect the adverse health effects of multiple toxic chemicals may be more important than focusing on the dose level of a single chemical. The invaders/defenders concept also leads to the realization that adverse health effects may not only be the result of exogenous exposures—if there is a steady stream of endogenous invaders from normal metabolic processes, depletion of defenses will also result in disease. It is not generally known how often this occurs because nonspecific insults such as stress can also affect the body's defense system.

Consideration of invaders and defenders in dose–response modeling is not merely an academic exercise. We now have the dose-response modeling tools to explore the qualitative and quantitative impact of a variety of combinations of the components of the invaders/defenders phenomenon that may lead to a range of dose–response shapes. These tools can be an important part of more biologically based dose–response estimation as well as being useful in generating research strategies. We hope that this paper will stimulate such pursuits.

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